



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : C07D 209/48, C07C 323/60, 327/32, A61K 31/18, 31/22, 31/40</p>	<p>A1</p>	<p>(11) International Publication Number: <b>WO 97/37973</b> (43) International Publication Date: 16 October 1997 (16.10.97)</p>
<p>(21) International Application Number: PCT/GB97/00957 (22) International Filing Date: 4 April 1997 (04.04.97) (30) Priority Data: 9607119.6 4 April 1996 (04.04.96) GB (71) Applicant (for all designated States except US): CHIRO-SCIENCE LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BAXTER, Andrew, Douglas [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). OWEN, David, Alan [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). MONTANA, John, Gary [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). WATSON, Robert, John [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). KEILY, John, Fraser [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).</p>		<p>(74) Agent: GILL JENNINGS &amp; EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB). (81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: PEPTIDYL COMPOUNDS HAVING MMP AND TNF INHIBITORY ACTIVITY (57) Abstract Compounds of formula (I) having MMP and TNF inhibitory activity.</p> <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>		

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PEPTIDYL COMPOUNDS HAVING MMP AND TNF INHIBITORY  
ACTIVITY

Field of the Invention

This invention relates to a novel class of peptidyl derivatives, to processes for  
5 their preparation, and to their use in medicine.

Background to the Invention

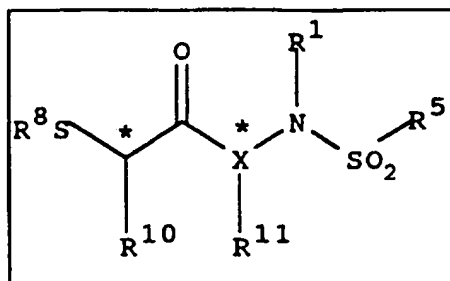
Metalloproteinases, including matrix metalloproteinase (MMP), (human  
fibroblast) collagenase, gelatinase and TNF convertase (TACE), and their modes of  
action, and also inhibitors thereof and their clinical effects, are described in WO-A-  
10 9611209, PCT/GB96/02438 and PCT/GB96/02892, the contents of which are  
incorporated herein by reference. MMP inhibitors may also be useful in the inhibition of  
other mammalian metalloproteinases such as the adamalysin family (or ADAMs) whose  
members include TNF convertase (TACE) and ADAM-10, which can cause the release  
of TNF $\alpha$  from cells, and others, which have been demonstrated to be expressed by  
15 human articular cartilage cells and also involved in the destruction of myelin basic  
protein, a phenomenon associated with multiple sclerosis.

Compounds which have the property of inhibiting the action of  
metalloproteinases involved in connective tissue breakdown, such as collagenase,  
stromelysin and gelatinase, have been shown to inhibit the release of TNF both *in vitro*  
20 and *in vivo*. See Gearing *et al* (1994), Nature 370:555-557; McGeehan *et al* (1994),  
Nature 370:558-561; GB-A-2268934; and WO-A-9320047. All of these reported  
inhibitors contain a hydroxamic acid zinc-binding group, as do the imidazole-substituted  
compounds disclosed in WO-A-9523790. Other compounds that inhibit MMP and/or  
TNF are described in WO-A-9513289, WO-A-9611209, WO-A-96035687, WO-A-  
25 96035711, WO-A-96035712 and WO-A-96035714.

Summary of the Invention

The invention encompasses novel mercaptoalkylacyl compounds of formula  
(I) which are useful inhibitors of matrix metalloproteinases and/or TNF $\alpha$ -mediated  
diseases including degenerative diseases (such as defined above) and certain cancers.

30 Novel compounds according to the invention are of general formula (I):



5 (I)

wherein:

X is CH or N;

R<sup>1</sup> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, aryl, C<sub>1-6</sub> alkyl-aryl, heteroaryl, C<sub>1-6</sub> alkyl-heteroaryl, cyclo(C<sub>3-6</sub>) alkyl, C<sub>1-6</sub> alkyl-cyclo(C<sub>3-6</sub>)alkyl, heterocyclo(C<sub>4-6</sub>)alkyl, C<sub>1-6</sub> alkyl-heterocyclo(C<sub>4-6</sub>)alkyl, C<sub>1-6</sub> alkyl-COR<sup>2</sup>, or C<sub>1-6</sub> alkyl-AR<sup>3</sup> group where A is O, NR<sup>3</sup> or S(O)<sub>n</sub> where n = 0-2 and R<sup>3</sup> is H, C<sub>1-4</sub> alkyl, aryl, heteroaryl, C<sub>1-4</sub> alkyl-aryl or C<sub>1-4</sub> alkyl-heteroaryl; if A = NR<sup>3</sup> the groups R<sup>3</sup> may be the same or different;

R<sup>2</sup> is OR<sup>4</sup> or N(R<sup>4</sup>)<sub>2</sub> where each R<sup>4</sup> may be the same or different;

15 R<sup>4</sup> is H or C<sub>1-4</sub> alkyl;

R<sup>5</sup> is aryl (optionally substituted with R<sup>6</sup>), heteroaryl (optionally substituted with R<sup>6</sup>), C<sub>1-4</sub> alkyl-aryl (optionally substituted with R<sup>6</sup>), C<sub>1-4</sub> alkyl-heteroaryl (optionally substituted with R<sup>6</sup>), C<sub>1-4</sub> alkyl (optionally substituted with R<sup>6</sup>), cyclo(C<sub>3-6</sub>) alkyl (optionally substituted with R<sup>6</sup>), C<sub>1-4</sub> alkyl-cyclo(C<sub>3-6</sub>)alkyl (optionally substituted with R<sup>6</sup>), heterocyclo(C<sub>4-6</sub>)alkyl (optionally substituted with R<sup>6</sup>) or C<sub>1-4</sub> alkyl-heterocyclo(C<sub>4-6</sub>)alkyl (optionally substituted with R<sup>6</sup>);

R<sup>6</sup> is halogen, C<sub>1-6</sub> alkyl, aryl, heteroaryl, AR<sup>3</sup>, NR<sup>3</sup>R<sup>7</sup>, COR<sup>9</sup>, SO<sub>2</sub>N(R<sup>3</sup>)<sub>2</sub> where each R<sup>3</sup> may be the same or different, CO<sub>2</sub>R<sup>4</sup>, CON(R<sup>3</sup>)<sub>2</sub> where each R<sup>3</sup> may be the same or different, amidine or guanidine;

25 R<sup>7</sup> is COR<sup>20</sup>, CO<sub>2</sub>R<sup>19</sup>, SO<sub>2</sub>R<sup>9</sup> or CO(NR<sup>3</sup>)<sub>2</sub> where each R<sup>3</sup> may be the same or different;

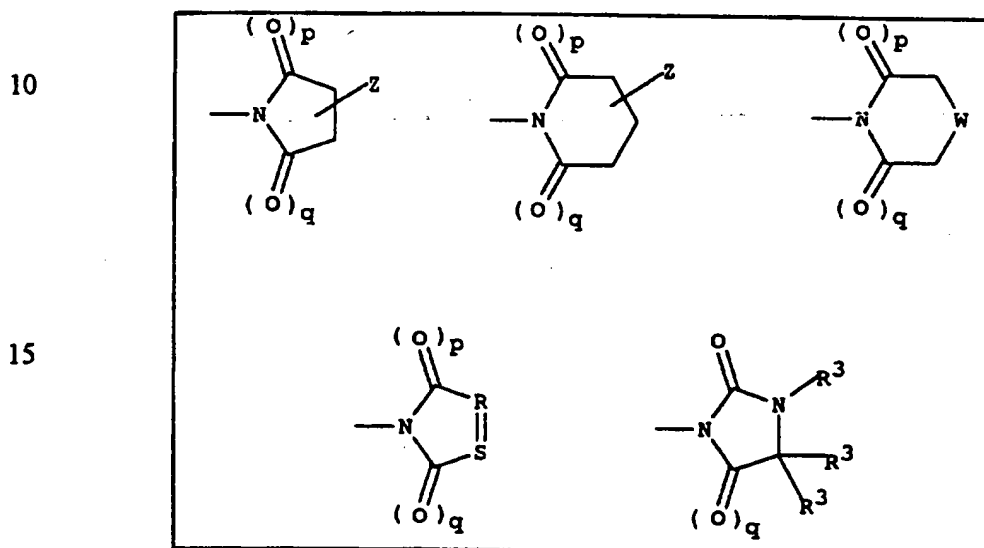
R<sup>8</sup> is H or COR<sup>9</sup>;

R<sup>9</sup> is C<sub>1-4</sub> alkyl, aryl, heteroaryl, C<sub>1-4</sub> alkyl-aryl or C<sub>1-4</sub> alkyl-heteroaryl;

30 R<sup>10</sup> and R<sup>11</sup> are the same or different and are each H, C<sub>1-6</sub> alkyl (optionally substituted with R<sup>12</sup>), aryl (optionally substituted with R<sup>12</sup>), C<sub>1-6</sub> alkyl-aryl (optionally substituted with R<sup>12</sup>), heteroaryl (optionally substituted with R<sup>12</sup>), C<sub>1-6</sub> alkyl-heteroaryl

(optionally substituted with  $R^{12}$ ), cyclo( $C_{3-6}$ ) alkyl (optionally substituted with  $R^{12}$ ),  $C_{1-6}$  alkyl-cyclo( $C_{3-6}$ )alkyl (optionally substituted with  $R^{12}$ ), heterocyclo( $C_{4-6}$ )alkyl (optionally substituted with  $R^{12}$ ) or  $C_{1-4}$  alkyl-heterocyclo( $C_{4-6}$ )alkyl (optionally substituted with  $R^{12}$ );

- 5  $R^{12}$  is  $SO_2R^9$ ,  $SO_2N(R^3)_2$  where each  $R^3$  may be the same or different,  $SR^8$ ,  $COR^{13}$ ,  $N(R^3)_2$  where each  $R^3$  may be the same or different,  $NR^3R^{14}$ ,  $OR^3$ , phthalimido or the groups:



20

$p$  and  $q$  are each 0 or 1 and may be the same or different;

$R$  and  $S$  are each  $CH$  or  $N$  and may be the same or different;

$W$  is  $O$ ,  $S(O)_n$  where  $n = 0-2$ , or  $NR^{15}$ ;

- 25  $Z$  is  $H$  or  $C_{0-4}$  alkyl- $R^{18}$  and may be attached to any available position on the ring;

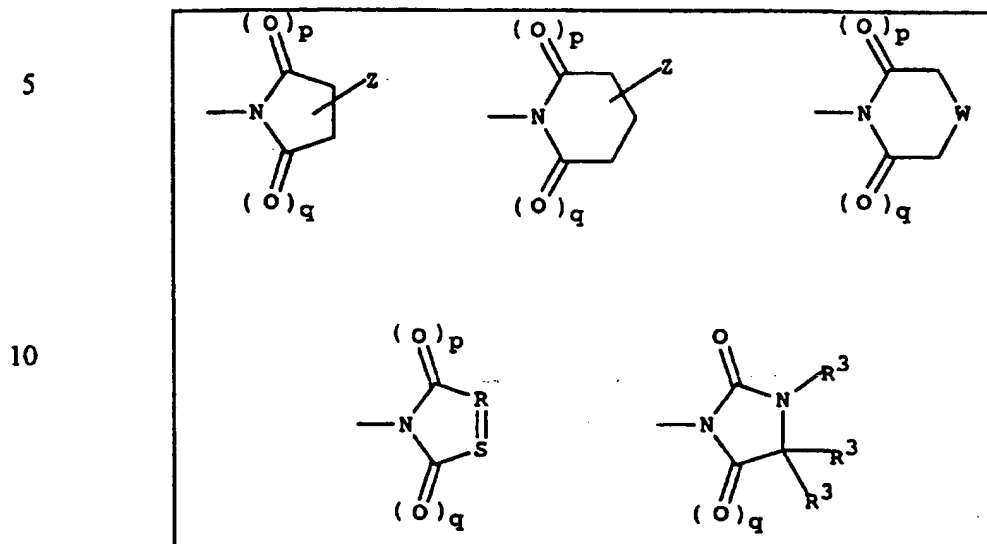
$R^{13}$  is  $OR^{20}$ ,  $N(R^3)_2$  where  $R^3$  may be the same or different,  $C_{1-4}$  alkyl, aryl,  $C_{1-4}$  alkyl-aryl, heteroaryl or  $C_{1-4}$  alkyl-heteroaryl;

$R^{14}$  may be any group defined in  $R^7$  or  $COR^{16}$ ;

- 30  $R^{15}$  is  $H$ ,  $C_{1-4}$  alkyl,  $COR^9$ ,  $CO_2R^{19}$ ,  $CON(R^3)_2$  where each  $R^3$  may be the same or different, or  $SO_2R^9$ ;

$R^{16}$  is  $C_{1-4}$  alkyl- $R^{17}$ ;

$R^{17}$  is  $\text{CO}_2R^4$ ,  $\text{CON}(R^3)_2$  where each  $R^3$  may be the same or different,  $\text{N}(R^3)_2$  where each  $R^3$  may be the same or different,  $\text{SO}_2R^9$  or the groups:



15  $R^{18}$  is  $\text{CO}_2R^3$ ,  $\text{CON}(R^3)_2$  where each  $R^3$  may be the same or different,  $\text{N}(R^3)_2$  where each  $R^3$  may be the same or different,  $\text{NHCO}_2R^{19}$ ,  $\text{NHCO}_2R^9$  or  $\text{NHCOR}^9$ ;  
 $R^{19}$  is  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkyl-aryl or  $\text{C}_{1-4}$  alkyl-heteroaryl;  
 $R^{20}$  is H,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkyl-aryl or  $\text{C}_{1-4}$  alkyl-heteroaryl;  
 and the salts, solvates and hydrates thereof.

20 Combinations of substituents and/or variables are only permissible if such combinations result in stable compounds.

#### Description of the Invention

Preferred compounds of the invention are those wherein any one or more of the following apply:

25 X is N;

$R^1$  is  $\text{C}_{1-6}$  alkyl or  $\text{C}_{1-6}$  alkylaryl,  $\text{C}_{1-6}$  alkylheteroaryl,  $\text{C}_{1-6}$  alkyl-COR<sup>2</sup> or  $\text{C}_{2-6}$  alkyl-AR<sup>3</sup>, and A is O or S(O)<sub>0-2</sub>;

$R^2$  is OR<sup>4</sup> or N(R<sup>4</sup>)<sub>2</sub>;

$R^3$  is  $\text{C}_{1-4}$  alkyl, aryl or  $\text{C}_{1-6}$  alkylaryl;

30  $R^4$  is H or  $\text{C}_{1-4}$  alkyl;

R<sup>5</sup> is aryl (optionally substituted with R<sup>6</sup>) or heteroaryl (optionally substituted with R<sup>6</sup>);

R<sup>6</sup> is AR<sup>3</sup>;

R<sup>9</sup> is alkyl or aryl;

5 R<sup>10</sup> and R<sup>11</sup> are the same or different and are each H or C<sub>1-6</sub> alkyl (optionally substituted with R<sup>12</sup>); and

R<sup>12</sup> is phthalimido, succinimido or 3,4,4-trimethylhydantoin.

The compounds of the Examples are particularly preferred.

It will be appreciated that the compounds according to the invention can  
10 contain one or more asymmetrically-substituted carbon atoms, for example those marked with an asterisk in formula (I). The presence of one or more of these asymmetric centres in a compound of formula (I) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures  
15 thereof.

In the formulae herein, the ~ line is used at a potential asymmetric centre to represent the possibility of *R*- and *S*- configurations, the < line and the ..... line to represent a unique configuration at an asymmetric centre.

As used in this specification, alone or in combination, the term "C<sub>1-6</sub> alkyl"  
20 refers to straight or branched chain alkyl moiety having from one to seven carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl and the like.

The term "C<sub>1-4</sub> alkyl" refers to a straight or branched chain alkyl moiety having from one to four carbon atoms, including for example, methyl, ethyl, propyl,  
25 isopropyl, butyl, *tert*-butyl and the like.

The term "C<sub>2-6</sub> alkenyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one double bond, of either *E* or *Z* stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2- butenyl, 2-methyl-2-propenyl etc.

The term "cyclo ( $C_{3-6}$ ) alkyl" refers to a saturated alicyclic moiety having from three to six carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "heterocyclo ( $C_{4-6}$ ) alkyl" refers to a saturated heterocyclic moiety  
5 having from three to six carbon atoms and one or more heteroatom from the group N, O, S and includes for example azetidiny, pyrrolidinyl, tetrahydrofuranyl, piperidinyl and the like.

The term "aryl" means an optionally substituted phenyl or naphthyl group with the substituent(s) being selected, for example, from halogen, trifluoromethyl,  $C_{1-6}$   
10 alkyl, alkoxy, phenyl and the like.

The term "heteroaryl" refers to aromatic ring systems of five to ten atoms or which at least one atom is selected from the group, O, N, or S and includes for example furanyl, thiophenyl, pyridyl, indolyl, quinolyl and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The terms "protected amino" and "protected carboxy" mean amino and  
15 carboxy groups which are protected in a manner familiar to those skilled in the art. For example, an amino group can be protected by a benzyloxycarbonyl, *tert*-butoxycarbonyl, acetyl or like groups, or in the form of a phthalimido or like group. A carboxyl group can be protected in the form of a readily cleavable ester such as the  
20 methyl, ethyl, benzyl or *tert*-butyl ester.

Salts of compounds of formula (I) include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, such as hydrochlorides, hydrobromides, p-toluenesulphonates, phosphates, sulphates, perchlorates, acetates, trifluoroacetates, propionates, citrates, malonates, succinates,  
25 lactates, oxalates, tartrates and benzoates.

Salts may also be formed with bases. Such salts include salts derived from inorganic or organic bases, for example alkali metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

When the "protected carboxy" group in compounds of the invention is an  
30 esterified carboxyl group, it may be a metabolically labile ester of formula  $CO_2R^{21}$



where R<sup>21</sup> may be an ethyl, benzyl, phenethyl, phenylpropyl, α- or β-naphthyl, 2,4-dimethylphenyl, 4-*tert*-butylphenyl, 2,2,2-trifluoroethyl, 1-(benzyloxy)benzyl, 1-(benzyloxy)ethyl, 2-methyl-1-propionyloxypropyl, 2,4,6-trimethylbenzyloxymethyl or pivaloyloxymethyl group.

- 5 Compounds of the general formula (I) may be prepared by any suitable method known in the art and/or by the following processes.

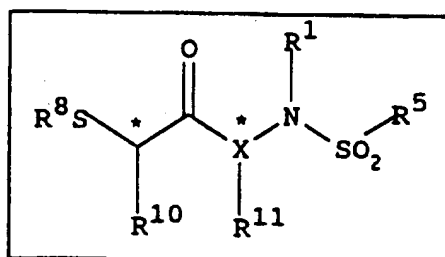
It will be appreciated that where a particular stereoisomer of formula (I) is required, the synthetic processes described herein may be used with the appropriate homochiral starting material and/or isomers may be resolved from mixtures using  
10 conventional separation techniques (e.g. HPLC).

The compounds according to the invention may be prepared by the following process. In the description and formulae below the groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and R<sup>21</sup>, A, R, S, W, X, and Z are as defined above, except where otherwise indicated. It will be appreciated  
15 that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to be in protected form before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific  
20 details see Greene *et al*, "Protective Groups in Organic Synthesis", Wiley Interscience.

A process for preparing compounds of general formula (I) comprises deprotecting (for example by hydrolysis) a compound of general formula (II)

25

(II)



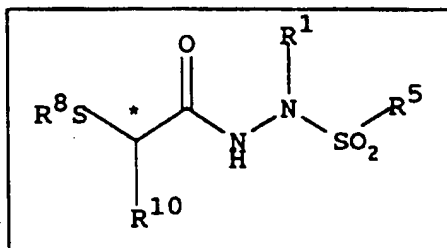
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wherein  $R^8$  represents a suitable protecting group (e.g. *tert*-butyl, trityl, benzoate or acetate).

It will be appreciated that where a particular stereoisomer of formula (I) is required, this may be obtained by conventional resolution techniques such as high performance liquid chromatography. Where desired, however, appropriate homochiral starting materials may be used in the coupling reaction to yield a particular stereoisomer of formula (I). This is exemplified below.

When  $X = N$ , and  $R^{11}$  is not aryl or heteroaryl, intermediates of general formula (II) may be prepared by alkylation of a hydrazide of formula (III)

(III)

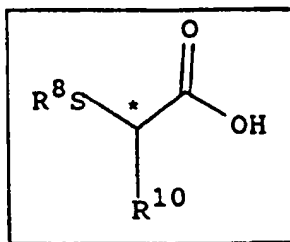


wherein  $R^1$ ,  $R^5$ ,  $R^{10}$  and  $R^8$  are as defined above, or an active derivative thereof, with an alkylating agent the formula  $B-R^{11}$  (IV) wherein B represents a suitable leaving group (e.g. a halogen such as bromide, or an alkylsulphonate ester such as methanesulphonate).

Alkylating agents of general formula (IV) may be obtained from commercially available starting materials using methods known to those skilled in the art. Many alkylating agents of general formula (IV) are also commercially available.

Hydrazides of general formula (III) may be prepared by coupling of an acid of general formula (V) or an activated derivative thereof,

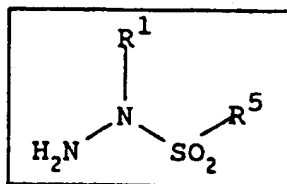
30 (V)



with a hydrazine derivative of general formula (VI).

5

(VI)



Active derivatives of acids of formula (V) include for example acid anhydrides  
10 or acid halides, such as acid chlorides.

The coupling reaction may be performed using standard conditions for  
amination reactions of this type. Thus, the reaction may be achieved in a solvent, for  
example an inert organic solvent such as an ether, e.g. a cyclic ether such as  
tetrahydrofuran, an amide e.g. a substituted amide such as dimethylformamide, or a  
15 halogenated hydrocarbon such as dichloromethane at a low temperature e.g. -30°C to  
ambient temperature, such as -20°C to 0°C, optionally in the presence of as base, e.g.  
an organic base such as an amine, e.g. triethylamine or a cyclic amine such as *N*-  
methylmorpholine. Where an acid of formula (V) is used, the reaction may  
additionally be performed in the presence of a condensing agent, for example a  
20 diimide such as *N,N'*-dicyclohexylcarbodiimide, advantageously in the presence of a  
triazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with  
a chloroformate for example ethylchloroformate, prior to reaction with the amine of  
formula (VI).

Acids of formula (V) may be prepared according to the procedure described  
25 in WO-A-9611209.

An intermediate of general formula (VI) may be prepared by reaction of a  
hydrazine of the formula R¹-NH-NH₂ (VII) with a sulphonyl chloride of the formula  
R⁵-SO₂Cl (VIII), followed by removal of any protecting groups.

If R¹ is aryl or heteroaryl, the terminal nitrogen of the hydrazine will first need  
30 protecting. Suitable protecting groups include *tert*-butoxycarbonyl (Boc) and  
benzyloxycarbonyl (Cbz).

Hydrazines of general formula (VII) may be obtained from commercially available starting materials using methods known to those skilled in the art. Many hydrazines of general formula (VII) are also commercially available.

Sulphonyl chlorides of general formula (VIII) also may be obtained from  
5 commercially available starting materials using methods known to those skilled in the art. Many compounds of general formula (VIII) are also commercially available.

If  $R^{11}$  is aryl or heteroaryl, a different procedure is required. Consequently, hydrazides of general formula (II) may be prepared by coupling of an acid of general formula (V) or an active derivative thereof, with a hydrazine derivative of the formula  
10  $R^{11}-NH-NR^1-SO_2R^5$  (IX).

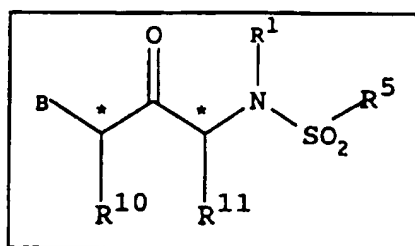
Active derivatives of acids of formula (V) include for example acid anhydrides or acid halides, such as acid chlorides.

Providing  $R^1$  is not aryl or heteroaryl, intermediates of general formula (IX) may be prepared by reaction of a hydrazine of the formula  $R^1-NH-NH-R^{11}$  (X) with  
15 a sulphonyl chloride of formula (VIII).

Intermediates of general formula (X) may be prepared by alkylation of a hydrazine of the formula  $R^{11}-NHNH_2$  (XI) with an alkylating agent of the formula  $R^1-B$  (XII) wherein B is as defined above. Hydrazines of formula (XI) and alkylating agents of general formula (XII) may be obtained from commercially available starting  
20 materials using methods known to those skilled in the art. Many hydrazines of formula (XI) and alkylating agents of general formula (XII) are also commercially available.

When  $X = CH$  and  $R^1$  is not aryl or heteroaryl, intermediates of general formula (II) may be prepared by nucleophilic displacement by a thiol of the formula  
25  $R^8SH$  (XIII) wherein  $R^8$  represents a suitable protecting group (e.g. *tert*-butyl, trityl, benzoyl or acetate), prepared using standard conditions known to those skilled in the art as exemplified by WO-A-9005719, with an alkylating agent of general formula (XVI)

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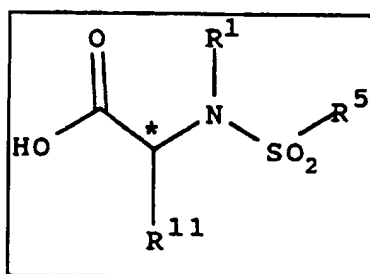


5

wherein B is as defined previously.

Thiols of general formula (XIII) may be obtained from commercially available starting materials using methods known to those skilled in the art. Many thiols of general formula (XIII) are also commercially available.

10 When  $R^{10}$  is H and B is bromide, intermediates of formula (XIV) may be prepared by reaction of an activated derivative of an acid of general formula (XV)



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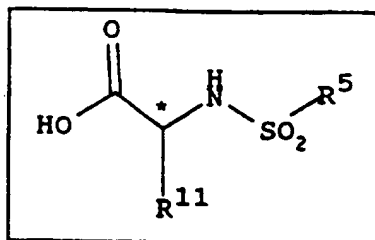
(XV)

with diazomethane, followed by quenching the intermediate diazoketone with  
20 hydrobromic acid.

Active derivatives of acids of formula (XV) include for example acid anhydrides or acid halides, such as acid chlorides.

Acids of general formula (XV) may be prepared by alkylation of amino acid derivatives of formula (XVI) with an alkylating agent of general formula (XII).

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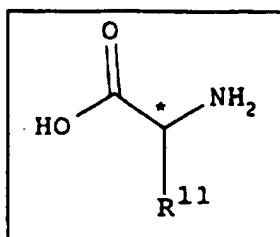


(XVI)

30 Such amino acid derivatives may in turn be prepared by reaction of an amino acid of general formula (XVII)

12

(XVII)



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with a sulphonyl chloride of formula (VIII).

When  $R^{10}$  is required to be a group other than hydrogen, suitably protected compounds of general formula (II) may be prepared by deprotonation then alkylation of the parent compound (II) where  $R^{10}$  is hydrogen, with an alkylating agent of the formula  $R^{10}$ -B (XVIII) wherein B is as defined previously.

Alkylating agents of general formula (XVIII) may be obtained from commercially available starting materials using methods known to those skilled in the art. Many alkylating agents of general formula (XVIII) are also commercially available.

Compounds of formula (I) may also be prepared by interconversion of other compounds of formula (I). Thus, for example, a compound of formula (I) wherein  $R^1$  is a  $C_{1-6}$  alkyl group may be prepared by hydrogenation (using palladium on carbon in suitable solvent, such as an alcohol - e.g. ethanol) of a compound of formula (I) wherein  $R^1$  is a  $C_{2-6}$  alkenyl group. A further example would include a compound of formula (I) wherein  $R^8$  is a group  $R^9$  CO may be prepared by acylation (using a suitable acid chloride  $R^9$  COCl, in the presence of a base such as a triethylamine in a suitable solvent, such as a chlorinated solvent - e.g. dichloromethane) of a compound of formula (I) wherein  $R^8$  is H.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallization, or by formation of a salt if appropriate or possible under the circumstances.

The compounds according to the invention exhibit *in vitro* inhibiting activities with respect to stromelysin, collagenase and gelatinase. Compounds according to the

invention also exhibit *in vitro* inhibition of TNF release. The activity and selectivity of the compounds may be determined by use of the appropriate enzyme inhibition test, for example as described in WO-A-9611209 or PCT/GB96/02892.

This invention also relates to a method of treatment for patients (including man  
5 and/or mammalian animals raised in the dairy, meat or fur industries or as pets) suffering from disorders or diseases which can be attributed to stromelysin as previously described and, more specifically, a method of treatment involving the administration of the matrix metalloproteinase inhibitors of formula (I) as the active constituents.

10 Accordingly, the compounds of formula (I) can be used among other things in the treatment of osteoarthritis and rheumatoid arthritis, and in diseases and indications resulting from the over-expression of these matrix metalloproteinases such as found in certain metastatic tumour cell lines.

As mentioned above, compounds of formula (I) are useful in human or  
15 veterinary medicine since they are active as inhibitors of TNF and MMPs.

Accordingly in another aspect, this invention concerns:

a method of management (by which is meant treatment or prophylaxis) of disease or conditions mediated by TNF and/or MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective, amount  
20 of a compound of formula (I) above, or a pharmaceutically acceptable salt thereof; and

- a compound of formula (I) for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs; and

25 the use of a compound of formula (I) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs.

The disease or conditions referred to above include inflammatory diseases, autoimmune diseases cancer, cardiovascular diseases, diseases involving tissue  
30 breakdown such as rheumatoid arthritis, osteoarthritis, osteoporosis, neurodegeneration, Alzheimer's disease, atherosclerosis, congestive heart failure,

stroke, vasculitis, Crohn's disease, ulcerative colitis, multiple sclerosis, periodontitis, gingivitis and those involving tissue breakdown such as bone resorption, haemorrhage, coagulation, acute phase response, cachexia and anorexia, acute infections, HIV infections, fever, shock states, graft versus host reactions, dermatological conditions, surgical wound healing, psoriasis, atopic dermatitis, epidermolysis bullosa, tumour growth, angiogenesis and invasion by secondary metastases, ophthalmological disease, retinopathy, corneal ulceration, reperfusion injury, migraine, meningitis, asthma, rhinitis, allergic conjunctivitis, eczema, anaphylaxis, restenosis, congestive heart failure, endometriosis, atherosclerosis and endosclerosis.

10 For the treatment of rheumatoid arthritis, osteoarthritis, and in diseases and indications resulting from the over-expression of matrix metalloendoproteinases such as found in certain metastatic tumour cell lines or other diseases mediated by the matrix metalloendoproteinases or increased TNF production, the compounds of formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally  
15 in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats etc, the compounds of the invention are effective in the  
20 treatment of humans.

The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to  
25 any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable  
30 excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose,



calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay  
5 disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the US Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

10 Formulations for oral use may also be presented as hard gelatin capsules where in the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

15 Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for  
20 example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such a polyoxyethylene with partial esters derived from fatty acids and  
25 hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a  
30 vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening

agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

5           Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified, for example sweetening, flavouring and colouring agents, may also be present.

10           The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soya bean, lecithin,  
15           and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

          Syrups and elixirs may be formulated with sweetening agents, for example  
20           glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been  
25           mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or  
30           suspending medium. For this purpose any bland fixed oil may be employed including

synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc containing the compounds of Formula (I) are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.05 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above- indicated conditions (about 2.5 mg to about 7 gms per patient per day). for example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 0.5 mg to about 3.5 gms per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following Examples illustrate the invention.

In the Examples, the following abbreviations are used:

TNF $\alpha$             Tumour Necrosis Factor  $\alpha$

LPS	Lipopolysaccharide
ELISA	Enzyme linked immunosorbant assay
EDC	1-Ethyl-2-dimethylaminopropylcarbodiimide
RT	Room Temperature

5 **Intermediate 1**  $N^1 - [(4\text{-Methoxybenzene})\text{sulphonyl}] - N^1 -$   
**(phenylmethyl)hydrazine**

4-Methoxybenzenesulphonyl chloride (1.1 g, 5 mmol) was added to a suspension of benzylhydrazine dihydrochloride (1.0 g, 5 mmol) and triethylamine (1.5 g, 15 mmol) in tetrahydrofuran (40 ml) and the mixture was stirred at RT for 18 h. The thick white  
 10 suspension was evaporated *in vacuo*, the residue dissolved in dichloromethane (100 ml), washed with water and brine, then dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo* to a yellow solid. Purification by column chromatography eluting with dichloromethane/hexane/ether (2:2:1) to provide the title compound as a colourless solid (0.60 g, 40 %).  
 15 TLC  $R_f$  0.38 [ $\text{CH}_2\text{Cl}_2$ /hexane/ether (2:2:1)].

**Intermediate 2**  $N^2 - [(2S)\text{-bromo-5-phthalimidopentanoyl}] - N^1 - [(4\text{-methoxybenzene})\text{sulphonyl}] - N^1 -$   
**(phenylmethyl)hydrazine**

(2S)-Bromo-5-phthalimidopentanoic acid (WO-A-9611209; 0.35 g, 1.1 mmol) was added to a solution of Intermediate 1 (0.29 g, 1 mmol) in tetrahydrofuran at 0°C.  
 20 EDC (0.22 g) and *N*-hydroxybenzotriazole (0.15 g) were added to the mixture and the resulting suspension was stirred at RT for 5 h, then evaporated *in vacuo* and the residue dissolved in dichloromethane. The solution was washed with water and brine, then dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo* to a yellow solid. Purification by column chromatography eluting with dichloromethane/hexane/ether (2:2:1) to provide the title  
 25 compound as a colourless solid (0.15 g, 27 %).  
 TLC  $R_f$  0.22 [ $\text{CH}_2\text{Cl}_2$ /hexane/ether (2:2:1)]

**Intermediate 3** **(*R,S*)- *N*-[(4-Methoxybenzene)sulphonyl]valine**

4-Methoxybenzenesulphonyl chloride (10.6 g, 51 mmol) was added to a solution of valine (6g, 51 mmol) in dioxane (40 ml) and water (40 ml) containing triethylamine  
 30 (10 ml, 1.4 eq). The solution was stirred for 6 h, then evaporated *in vacuo* and the residue dissolved in dichloromethane. The solution was washed with 1N hydrochloric

acid, water and brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give the crude product. This was dissolved in dichloromethane (30 ml), extracted with aqueous sodium bicarbonate then the aqueous solution acidified to pH2 with 6N hydrochloric acid to precipitate the product. Filtration gave the title compound as colourless solid (3.65 g, 25 %).

TLC R<sub>f</sub> 0.42 (4 % AcOH-EtOAc)

**Intermediate 4** (R,S)-N-[(4-Methoxybenzene)sulphonyl]valine 1,1-dimethylethyl ester

A solution of Intermediate 3 (4.36 g, 15 mmol) was heated at reflux in a mixture of toluene (30 ml) and dimethylformamide di-*tert*-butyl acetal (14 ml) for 3 h. The solvent was evaporated *in vacuo* and the residue partitioned between dichloromethane and water. The solution was washed with water, sat. sodium bicarbonate and brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to provide the title compound as colourless solid (2.87 g, 55 %).

TLC R<sub>f</sub> 0.62 (ether)

**Intermediate 5** (R,S)-N-[(4-Methoxybenzene)sulphonyl]-N-(phenylmethyl)valine 1,1-dimethylethyl ester

Sodium hydride (0.20 g, 5 mmol) was added to a solution of Intermediate 4 (1.30 g, 3.8 mmol) in dimethylformamide (10 ml) at 0°C and the cloudy solution was stirred for 30 min, then benzyl bromide (0.71 g, 1.1 eq) was added dropwise and the solution stirred for a further 18 h at RT. The mixture was poured into water, extracted with ether, the combined extracts washed with water and brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give crude product as colourless oil. Purification by column chromatography, eluting with ether-hexane (1:2) provided the title compound as colourless solid (1.35 g, 82 %).

TLC R<sub>f</sub> 0.37 [ether-hexane (1:2)]

**Intermediate 6** (R,S)-N-[(4-Methoxybenzene)sulphonyl]-N-(phenylmethyl)valine

Trifluoroacetic acid (10 ml) was added to a solution of Intermediate 5 (1.34 g, 3.1 mmol) in dichloromethane at RT. The solution was stirred for 4 h, then evaporated

*in vacuo* and the residue azeotroped to dryness with hexanes to provide the title compound as colourless solid (1.15 g, 99 %).

TLC  $R_f$  0.62 (ether)

**Intermediate 7** (2*R,S*)-Bromomethyl-[2-[*N*-(4-methoxybenzene)sulphonyl]-*N*-(phenylmethyl)amino]-3-methylbutyl ketone

Ethyl chloroformate (0.12 g, 1.1 mmol) was added to a solution of Intermediate 6 (0.43 g, 1 mmol) in tetrahydrofuran (10 ml) and *N*-methylmorpholine (0.11 g, 1.1 mmol) at 0°C and the mixture was stirred for 2 h, then filtered into a dry Erlenmeyer flask. A solution of diazomethane (2.3 mmol) in ether (20 ml) was added and the solution stirred for 24 h. Hydrobromic acid (48%, 2 ml) and acetic acid (3 ml) were, the mixture stirred at RT for 1 h, then neutralised by addition of sat. sodium bicarbonate and extracted with ether. The combined extracts were washed with water and brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give a colourless oil. Purification by chromatography, eluting with ether-hexane (1:3) gave the title compound as colourless oil (78 mg, 15 %).

TLC  $R_f$  0.70 [ether-hexanes (1:1)]

**Example 1** *N*<sup>2</sup>-[(2*S*)-(Acetylmercapto)acetyl-5-phthalimidopentanoyl]-*N*<sup>1</sup>-[(4-methoxybenzene)sulphonyl]-*N*<sup>1</sup>-(phenylmethyl)hydrazine

Potassium thioacetate (0.20 g) was added to a solution of Intermediate 2 (0.12 g, 0.21 mmol) in methanol (10 ml) at RT and the solution was stirred for 3h. The mixture was then evaporated *in vacuo*, and the residue dissolved in dichloromethane. The solvent was washed with water and brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The residue was purified by column chromatography, eluting with dichloromethane/hexane/ether (1:1:1) to provide the title compound as a colourless solid (0.10 g, 80 %).

TLC  $R_f$  0.35 [CH<sub>2</sub>Cl<sub>2</sub>/hexane/ether (1:1:1)]

**Example 2** *N*<sup>2</sup>-[(Acetylthio)acetyl]-*N*<sup>1</sup>-[(4-methoxybenzene)sulphonyl]-*N*<sup>1</sup>-(phenylmethyl)hydrazine

Acetylthioacetyl chloride (0.15 g, 1 mmol) was added to a solution of Intermediate 1 (0.19 g, 0.65 mmol) in tetrahydrofuran (10 ml) and triethylamine (0.10 g, 1.5 eq) at 0°C. The brown suspension was stirred for 2 days at RT, then diluted with

$\text{CH}_2\text{Cl}_2$  (100 ml) and washed with 0.5 N hydrochloric acid, sat. sodium bicarbonate and brine, dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo*. The residue was purified by column chromatography, eluting with dichloromethane/hexane/ether (2:2:1) to give the title compound as a beige solid (0.025 g, 10 %).

5 TLC  $R_f$  0.19 [ $\text{CH}_2\text{Cl}_2$ /hexane/ether (2:2:1)]

**Example 3** 2-(Acetylmercapto)methyl-2-[N-[(4-methoxybenzene)sulphonyl]-N-(phenylmethyl)amino]-3-methylbutyl ketone

Potassium thioacetate (30 mg, 2 eq) was added to a solution of Intermediate 8 (60 mg) in methanol (5 ml) at RT and the solution was stirred for 3 h. The mixture was  
10 then evaporated *in vacuo* and the residue partitioned between water and dichloromethane. The solution was washed with brine, dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo* to provide the title compound as a pale yellow foam (46 mg, 78 %).

TLC  $R_f$  0.65 (ether)

**Example 4**  $N^2$ -(Mercaptoacetyl)- $N^1$ -[(4-methoxybenzene)sulphonyl]- $N^1$ -(phenylmethyl)hydrazine  
15

Aqueous ammonia (SG 0.88; 0.5 ml) was added to a solution of Example 2 (16 mg) in methanol (5 ml) at 0°C and the solution was stirred for 2 h then evaporated *in vacuo* and the residue dissolved in dichloromethane. The solution was washed with brine, dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo* to provide the title compound as a pale  
20 yellow solid (12 mg).

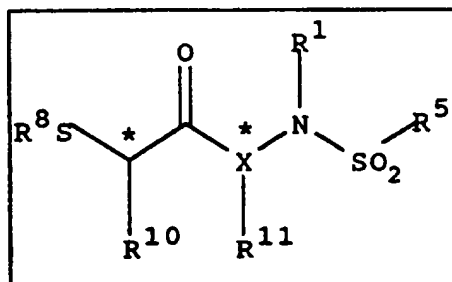
TLC  $R_f$  0.35 [ $\text{CH}_2\text{Cl}_2$ /hexane/ether (1:1:1)]

**CLAIMS**

1. A compound of general formula (I)

5

(I)



10

wherein:

X is CH or N;

- 15  $R^1$  is a  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl, aryl,  $C_{1-6}$  alkyl-aryl, heteroaryl,  $C_{1-6}$  alkyl-heteroaryl, cyclo( $C_{3-6}$ ) alkyl,  $C_{1-6}$  alkyl-cyclo( $C_{3-6}$ )alkyl, heterocyclo( $C_{4-6}$ )alkyl,  $C_{1-6}$  alkyl-heterocyclo( $C_{4-6}$ )alkyl,  $C_{1-6}$  alkyl-COR<sup>2</sup>, or  $C_{1-6}$  alkyl-AR<sup>3</sup> group where A is O, NR<sup>3</sup> or S(O)<sub>n</sub> where n = 0-2 and R<sup>3</sup> is H,  $C_{1-4}$  alkyl, aryl, heteroaryl,  $C_{1-4}$  alkyl-aryl or  $C_{1-4}$  alkyl-heteroaryl; if A=NR<sup>3</sup> the groups R<sup>3</sup> may be the same or different;

R<sup>2</sup> is OR<sup>4</sup> or N(R<sup>4</sup>)<sub>2</sub> where each R<sup>4</sup> may be the same or different;

- 20 R<sup>4</sup> is H or  $C_{1-4}$  alkyl;

- R<sup>3</sup> is aryl (optionally substituted with R<sup>6</sup>), heteroaryl (optionally substituted with R<sup>6</sup>),  $C_{1-4}$  alkyl-aryl (optionally substituted with R<sup>6</sup>),  $C_{1-4}$  alkyl-heteroaryl (optionally substituted with R<sup>6</sup>),  $C_{1-4}$  alkyl (optionally substituted with R<sup>6</sup>), cyclo( $C_{3-6}$ ) alkyl (optionally substituted with R<sup>6</sup>),  $C_{1-4}$  alkyl-cyclo( $C_{3-6}$ )alkyl (optionally substituted with R<sup>6</sup>), heterocyclo( $C_{4-6}$ )alkyl (optionally substituted with R<sup>6</sup>) or  $C_{1-4}$  alkyl-heterocyclo( $C_{4-6}$ )alkyl (optionally substituted with R<sup>6</sup>);

R<sup>6</sup> is halogen,  $C_{1-6}$  alkyl, aryl, heteroaryl, AR<sup>3</sup>, NR<sup>3</sup>R<sup>7</sup>, COR<sup>9</sup>, SO<sub>2</sub>N(R<sup>3</sup>)<sub>2</sub> where each R<sup>3</sup> may be the same or different, CO<sub>2</sub>R<sup>4</sup>, CON(R<sup>3</sup>)<sub>2</sub> where each R<sup>3</sup> may be the same or different, amidine or guanidine;

- 30 R<sup>7</sup> is COR<sup>20</sup>, CO<sub>2</sub>R<sup>19</sup>, SO<sub>2</sub>R<sup>9</sup> or CO(NR<sup>3</sup>)<sub>2</sub> where each R<sup>3</sup> may be the same or different;

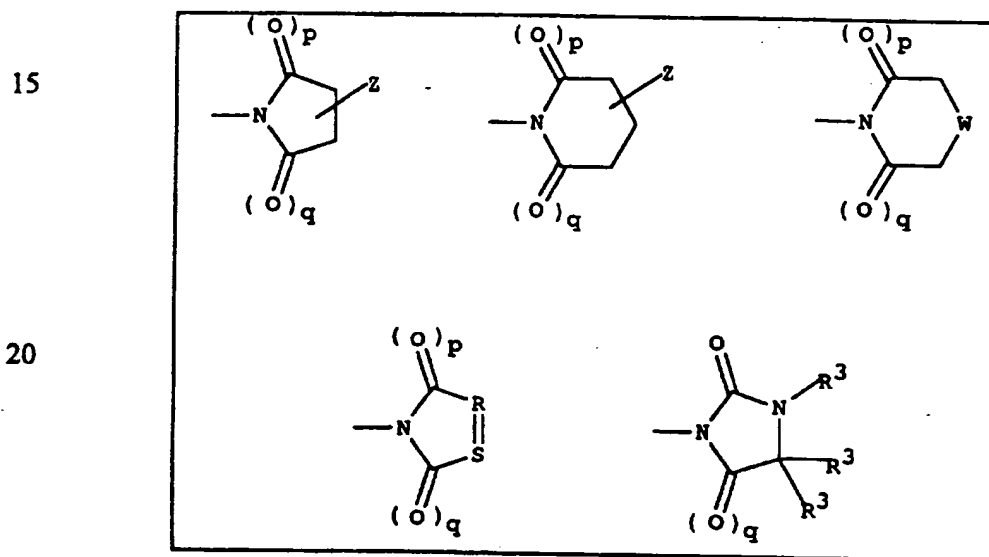


$R^8$  is H or  $COR^9$ ;

$R^9$  is  $C_{1-4}$  alkyl, aryl, heteroaryl,  $C_{1-4}$  alkyl-aryl or  $C_{1-4}$  alkyl-heteroaryl;

$R^{10}$  and  $R^{11}$  are the same or different and are each H,  $C_{1-6}$  alkyl (optionally substituted with  $R^{12}$ ), aryl (optionally substituted with  $R^{12}$ ),  $C_{1-6}$  alkyl-aryl (optionally substituted with  $R^{12}$ ), heteroaryl (optionally substituted with  $R^{12}$ ),  $C_{1-6}$  alkyl-heteroaryl (optionally substituted with  $R^{12}$ ), cyclo( $C_{3-6}$ ) alkyl (optionally substituted with  $R^{12}$ ),  $C_{1-6}$  alkyl-cyclo( $C_{3-6}$ )alkyl (optionally substituted with  $R^{12}$ ), heterocyclo( $C_{4-6}$ )alkyl (optionally substituted with  $R^{12}$ ) or  $C_{1-4}$  alkyl-heterocyclo( $C_{4-6}$ )alkyl (optionally substituted with  $R^{12}$ );

$R^{12}$  is  $SO_2R^9$ ,  $SO_2N(R^3)_2$  where each  $R^3$  may be the same or different,  $SR^8$ ,  $COR^{13}$ ,  $N(R^3)_2$  where each  $R^3$  may be the same or different,  $NR^3R^{14}$ ,  $OR^3$ , phthalimido or the groups:



25  $p$  and  $q$  are each 0 or 1 and may be the same or different;

$R$  and  $S$  are each CH or N and may be the same or different;

$W$  is O,  $S(O)_n$  where  $n = 0-2$ , or  $NR^{15}$ ;

$Z$  is H or  $C_{0-4}$  alkyl- $R^{18}$  and may be attached to any available position on the ring;

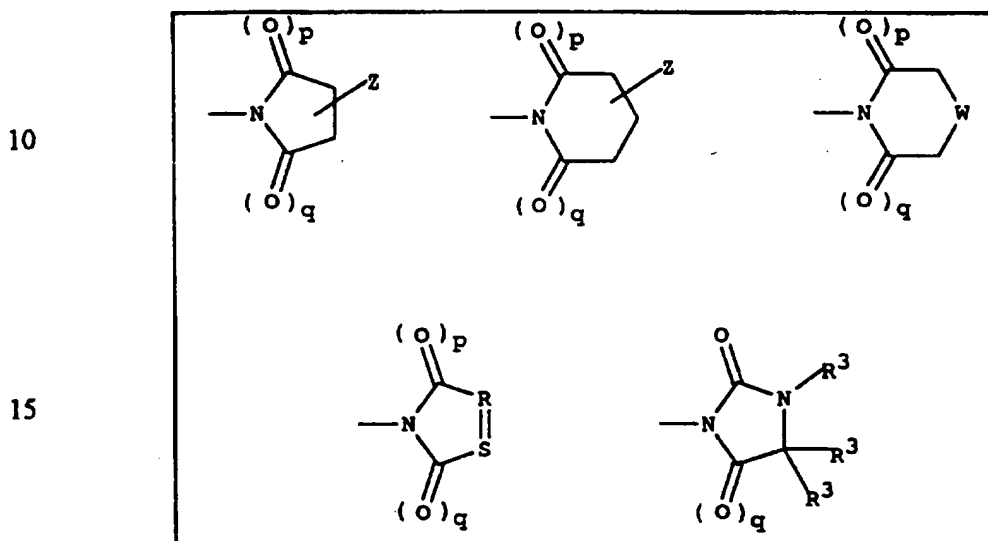
30  $R^{13}$  is  $OR^{20}$ ,  $N(R^3)_2$  where each  $R^3$  may be the same or different,  $C_{1-4}$  alkyl, aryl,  $C_{1-4}$  alkyl-aryl, heteroaryl or  $C_{1-4}$  alkyl-heteroaryl;

$R^{14}$  may be any group defined in  $R^7$  or  $COR^{16}$ ;

$R^{15}$  is H,  $C_{1-4}$  alkyl,  $COR^9$ ,  $CO_2R^{19}$ ,  $CON(R^3)_2$  where each  $R^3$  may be the same or different or  $SO_2R^9$ ;

$R^{16}$  is  $C_{1-4}$  alkyl- $R^{17}$ ;

5  $R^{17}$  is  $CO_2R^4$ ,  $CON(R^3)_2$  where each  $R^3$  may be the same or different,  $N(R^3)_2$  where each  $R^3$  may be the same or different,  $SO_2R^9$  or the groups:



$R^{18}$  is  $CO_2R^3$ ,  $CON(R^3)_2$  where each  $R^3$  may be the same or different,  $N(R^3)_2$

20 where each  $R^3$  may be the same or different,  $NHCO_2R^{19}$ ,  $NHSO_2R^9$  or  $NHCOR^9$ ;

$R^{19}$  is  $C_{1-4}$  alkyl,  $C_{1-4}$  alkyl-aryl or  $C_{1-4}$  alkyl-heteroaryl;

$R^{20}$  is H,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkyl-aryl or  $C_{1-4}$  alkyl-heteroaryl;

and the salts, solvates and hydrates thereof.

2. A compound of claim 1, wherein one or more of the following apply:

25 X is N;

$R^1$  is  $C_{1-6}$  alkyl or  $C_{1-6}$  alkylaryl,  $C_{1-6}$  alkylheteroaryl,  $C_{1-6}$  alkyl- $COR^2$  or  $C_{2-6}$  alkyl- $AR^3$ , and A is O or  $S(O)_{0-2}$ ;

$R^2$  is  $OR^4$  or  $N(R^4)_2$ ;

$R^3$  is  $C_{1-4}$  alkyl, aryl or  $C_{1-6}$  alkylaryl;

30  $R^4$  is H or  $C_{1-4}$  alkyl;

$R^5$  is aryl (optionally substituted with  $R^6$ ) or heteroaryl (optionally substituted with  $R_6$ );

$R^6$  is  $AR^3$ ;

$R^9$  is alkyl or aryl;

5  $R^{10}$  and  $R^{11}$  are the same or different and are each H or  $C_{1-6}$  alkyl (optionally substituted with  $R^{12}$ ); and

$R^{12}$  is phthalimido, succinimido or 3,4,4-trimethylhydantoin.

3. A compound of claim 1, selected from

10  $N^2$ -[(2S)-(Acetylmercapto)acetyl-5-phthalimidopentanoyl]- $N^1$ -[(4-methoxybenzene)sulphonyl]- $N^1$ -(phenylmethyl)hydrazine;

$N^2$ -[(Acetylthio)acetyl]- $N^1$ -[(4-methoxybenzene)sulphonyl]- $N^1$ -(phenylmethyl)hydrazine;

2-(Acetylmercapto)methyl-[2-[ $N$ -[(4-methoxybenzene)sulphonyl]- $N$ -(phenylmethyl)amino]-3-methyl]butyl ketone; and

15  $N^2$ -(Mercaptoacetyl)- $N^1$ -[(4-methoxybenzene)sulphonyl]- $N^1$ -(phenylmethyl)hydrazine.

4. A compound of any preceding claim, in the form of a single enantiomer or diastereomer.

5. A pharmaceutical composition for use in therapy, comprising a compound of  
20 any preceding claim, and a pharmaceutically-acceptable diluent, or carrier.

6. Use of a compound of any of claims 1 to 4, for the manufacture of a medicament for the treatment or prevention of a condition associated with matrix metalloproteinases or that is mediated by  $TNF\ \alpha$  or  $L$ -selectin sheddase.

7. Use according to claim 6, wherein the condition is selected from cancer,  
25 inflammation and inflammatory diseases, tissue degeneration, periodontal disease, ophthalmological disease, dermatological disorders, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia, anorexia, acute infection, HIV infection, shock states, graft versus host reactions, autoimmune disease, reperfusion injury, meningitis and migraine.

8. Use according to claim 6, wherein the condition is selected from tumour growth, angiogenesis, tumour invasion and spread, metastases, malignant ascites and malignant pleural effusion.
9. Use according to claim 6, wherein the condition is selected from cerebral  
5 ischaemia, ischaemic heart disease, rheumatoid arthritis, osteoarthritis, osteoporosis, asthma, multiple sclerosis, neurodegeneration, Alzheimer's atherosclerosis, stroke, vasculitis, Crohn's disease and ulcerative colitis.
10. Use according to claim 6, wherein the condition is selected from corneal ulceration, retinopathy and surgical wound healing.
- 10 11. Use according to claim 6, wherein the condition is selected from psoriasis, atopic dermatitis, chronic ulcers and epidermolysis bullosa.
12. Use according to claim 6, wherein the condition is selected from periodontitis and gingivitis.
13. Use according to claim 6, wherein the condition is selected from rhinitis,  
15 allergic conjunctivitis, eczema and anaphylaxis.
14. Use according to claim 6, wherein the condition is selected from restenosis, congestive heart failure, endometriosis, atherosclerosis and endosclerosis.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/00957

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D209/48 C07C323/60 C07C327/32 A61K31/18 A61K31/22  
A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 13289 A (CHIROSCIENCE) 18 May 1995 cited in the application see the whole document -----	1,5,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

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Date of the actual completion of the international search

9 July 1997

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/00957

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9513289 A	18-05-95	AU 8113394 A	29-05-95
		BR 9408025 A	17-12-96
		CN 1134705 A	30-10-96
		CZ 9601349 A	16-10-96
		EP 0728144 A	28-08-96
		FI 961976 A	09-05-96
		HU 73799 A	30-09-96
		NO 961888 A	09-05-96
		PL 314300 A	02-09-96
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